41. A Novel Approach towards 2,3,5-Trisubstituted Thiophenes *via* Tandem *Michael* Addition/Intramolecular *Knoevenagel* Condensation

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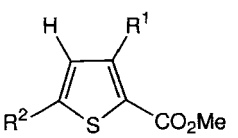
Starting from the easily available, highly functionalized acetylenic ketones **4a–i** (*Scheme 1*), novel 2,3,5-trisubstituted thiophenes **1a–i** (*Scheme 2*) were synthesized in good yields using a tandem *Michael*-addition/intramolecular *Knoevenagel*-condensation strategy, featuring $Cs_2CO_3/MgSO_4$ (1:2) as an efficient base to effect the cyclization. Subsequent simple one-step transformations yielded 2,3-disubstituted thiophene-5-carbaldehydes **7a–c**, carboxylic-acid derivatives **8**, **9**, and **11**, and alcohol **10** (*Scheme 3*). These molecules constitute interesting novel thiophene-containing building blocks, useful for the preparation of low-molecular-weight compound libraries by combinatorial and parallel-chemistry techniques.

Introduction. – The thiophene ring system has been widely studied in organic chemistry, and various substituted thiophenes have found many applications in the pharmaceutical field and, especially, in the search of new semiconductors [1]. Several different approaches towards this interesting class of compounds have been described, reaching from the classical *Hinsberg* [2] and *Gewald* [3] syntheses, the *Dieckmann* condensation of mercapto-ketone derivatives with alkynes [4] to electrocyclic reactions [5]. Recently, we have shown that acetylenic ketones are excellent precursors for the synthesis of substituted 3-bromothiophenes [6], substituted 3-bromopyrroles [7], substituted 3-halofurans [8], 2,2-dialkyl-2,3-dihydro-4*H*-pyran-4-ones [9], and 2,4-substituted quinolines [10]. In this paper, we present an alternative approach towards 2,3,5-trisubstituted thiophenes of type **1** using a tandem *Michael*-addition/intramolecular *Knoevenagel*-condensation strategy [11].



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Results and Discussions. – Our reaction sequence started by treatment of aldehydes **2a–f** with the alkynyllithium reagents derived from acetylenes **3a–f** to yield, after oxidation with MnO_2 in CH_2Cl_2 (*Method A*), the acetylenic ketones **4a–h** [6–10] [12] in generally good yields (*Scheme 1*).

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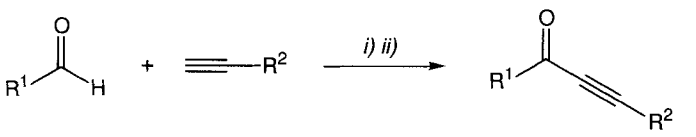
Scheme 1



2a–f **3a–f** **4a–i**

2 **a** R^1= Ph; **b** R^1= CF_3; **c** R^1= 4-$MeOCOC_6H_4$; **d** R^1= C_5H_{11}; **e** R^1= 3,4,5-$(MeO)_3C_6H_2$; **f** R^1= 

3 **a** R^2= $CH(OEt)_2$; **b** R^2= CH_2OTHP; **c** R^2= CO_2Me; **d** $CO_2(t\text{-Bu})$; **e** R^2= CH_2NHBoc **f** R^2= CH_2STr

4a R^1= Ph, R^2= $CH(OEt)_2$ [12] ; **b** R^1= CF_3, R^2= $CH(OEt)_2$; **c** R^1= 4-$MeOCOC_6H_4$, R^2= $CH(OEt)_2$; **d** R^1= C_5H_{11}, R^2= $CH(OEt)_2$ [12] ; **e** R^1= 3,4,5-$(MeO)_3C_6H_2$, R^2= CH_2OTHP [8] ; **f** R^1= 3, 4, 5-$(MeO)_3C_6H_2$, R^2= CO_2Me [9] ; **g** R^1=  , R^2= $CO_2(t\text{-Bu})$; **h** R^1= Ph, R^2= CH_2NHBoc [7] ; **i** R^1= Ph, R^2= CH_2STr [6] .

i) BuLi, THF, −78°, **3**; then **2**; *ii*) MnO_2, CH_2Cl_2, 0°–r.t. (*Method A*).

Products of type **4** could be easily prepared on large scale and were stable when stored in the freezer. Treatment of acetylenic ketones **4** with 1 equiv. of methylthioglycolate in THF at 0° resulted in the quantitative formation of an (*E*/*Z*)-mixture of *Michael* adducts **5** (*Scheme 2*) , which were transformed into the 2,3,5-trisubstituted thiophenes **1a–i**, isolated in 60–90% yields (*Scheme 2*) by addition of MeOH and 20 mol-% Cs_2CO_3 (mixed with predried $MgSO_4$) at 0° and stirring for 1–2 h at r.t.

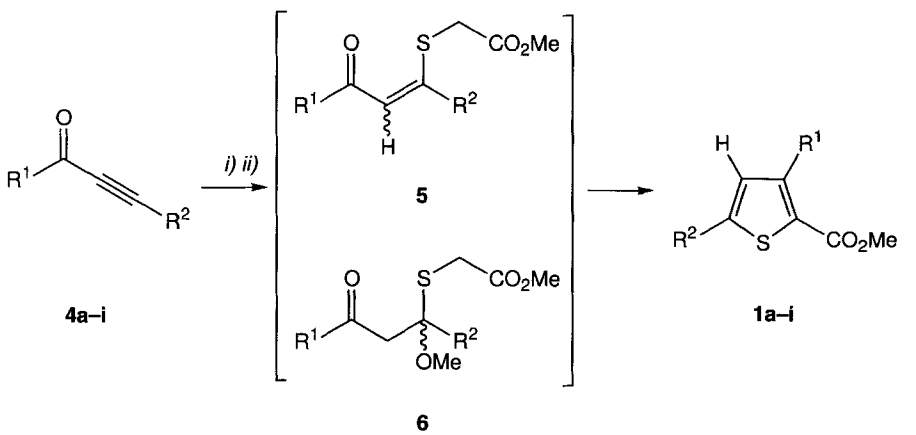
Addition of MeOH and Cs_2CO_3 to the reaction mixture proved to be essential for a fast intramolecular *Knoevenagel* condensation, presumably due to the intermediate formation of adducts of type **6** as indicated in *Scheme 2*. The use of 20 mol-% of DBU in DMF at room temperature was significantly less efficient for the cyclization step.

To demonstrate the utility of our approach towards an easy and versatile access to 2,3,5-trisubstituted thiophenes and their use as multifunctional building blocks, we performed subsequent one-step transformations as shown in *Scheme 3*.

The acetals **1a–c** could be easily converted into the corresponding aldehydes **7a–c** by treatment with 95% aqueous formic acid (*Method C*). The MeOCO group at C(2) of the thiophene moiety in compounds **1b** and **1e** were conveniently saponified using LiOH (3 equiv.) in THF/MeOH/H_2O 3:1:1 (*Method D*) to yield, after careful acidification (pH 2–3), the corresponding acids **8** and **9** in high yield. Conversely, selective deprotection of the THP group in **1e** under standard conditions gave alcohol **10** in 98% yield. Finally, the *tert*-butyl ester group in bis-ester **1g** was hydrolyzed specifically with TFA in CH_2Cl_2 to yield mono-acid **11** (98.5%).

Application of this reaction sequence towards substituted furans and pyrroles are under investigation and will be published in due course.

Scheme 2



1a R^1= Ph, R^2= $CH(OEt)_2$, **83%** ; **b** R^1= CF_3, R^2= $CH(OEt)_2$, **79%** ; **c** R^1=4-$MeOCOC_6H_4$, R^2= $CH(OEt)_2$, **82%** ; **d** R^1= C_5H_{11}, R^2= $CH(OEt)_2$, **84%** ; **e** R^1=3, 4, 5-$(MeO)_3C_6H_2$, R^2= CH_2OTHP, **85%** ; **f** R^1= 3,4,5-$(MeO)_3C_6H_2$, R^2= CO_2Me, **84.2%** ; **g** R^1=  R^2= CO_2tBu, **81.4%** ; **h** R^1= Ph, R^2= CH_2NHBoc, **89.5%** ; **i** R^1= Ph, R^2=CH_2STr, **58%.**

i) Methylthioglycolate, THF, 0°; *ii*) $CsCO_3/MgSO_4$ (1:2), MeOH, 0°–r.t. (*Method B*).

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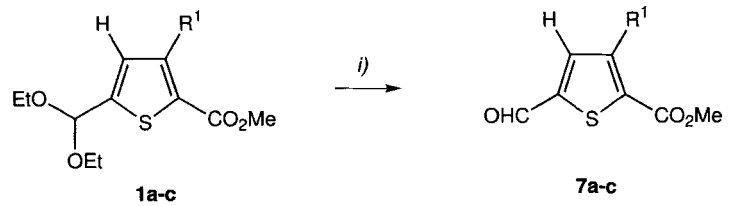
Experimental Part

General. See [8]. Compounds **4a** [12], **4d** [12], **4e** [8], **4f** [9], **4h** [7], and **4i** [6] have already been described. Compounds **3a–d** are commercially available; **3e** [8] and **3f** [6] have been described.

General Methods: *Method A.* To a stirred mixture of *3,3-diethoxyprop-1-yne* **3a** (5,0 ml, 34.9 mmol) in THF (80 ml) was added at −78° under Ar 24.0 ml of BuLi soln. (38.4 mmol, 1.6M in hexane). The mixture was stirred for 30 min at −78°, and a soln. of the corresponding aldehyde **2** (45.4 mmol) in THF (10 ml) was added, the mixture stirred for 1 h at −78°, slowly brought to −20°, and poured onto ice, 1M aq. NaH_2PO_4 soln. (50 ml), and AcOEt (150 ml). The org. layer was washed with sat. brine (80 ml), dried ($MgSO_4$), and the solvents were removed and the residue dried under reduced pressure. The crude residue was dissolved in CH_2Cl_2 (100 ml) and added, under Ar and ice-bath cooling to a suspension of MnO_2 (110 g) in 100 ml of CH_2Cl_2. The mixture was stirred for 1 h at 0°, filtered through a plug of *Celite* and $MgSO_4$, and the solvent was removed and the residue purified as indicated.

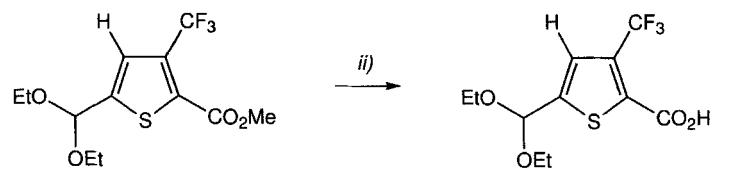
Method B. To a stirred soln. of 5.0 mmol of the corresponding acetylenic ketone **4** in THF (15 ml) was added under Ar and at 0° methylthioglycolate (0.46 ml, 5.0 mmol), and the mixture. was stirred for 2 h at 0°, followed by addition of MeOH (5 ml) and 5.0 g of $Cs_2CO_3/MgSO_4$ (1:2; pre-dried at 200° under reduced pressure). The suspension was stirred for 15 min at 0° and for 2 h at r.t., poured onto ice, 2N aq. NaH_2PO_4 soln. (80 ml), and AcOEt. The org. phase was extracted with AcOEt (2 × 100 ml), the comb. org. fractions were washed with sat. brine (100 ml), dried ($MgSO_4$), the solvents removed, and the residue was chromatographed on SiO_2 (120 g) with mixtures of AcOEt/hexane as indicated.

Scheme 3

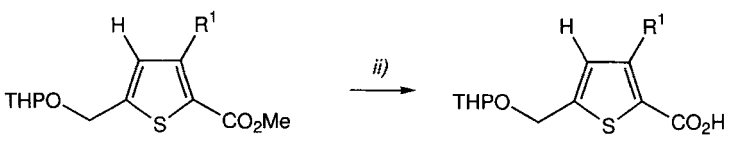


1a-c **7a-c**

a R^1= Ph ; **b** R^1= CF_3 ; **c** R^1= 4-MeOCOC$_6H_4$

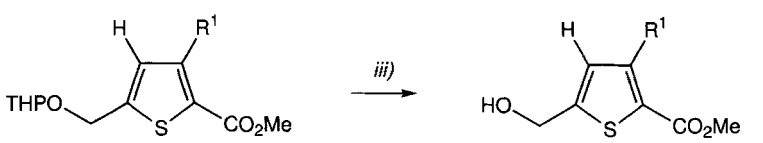


1b **8**



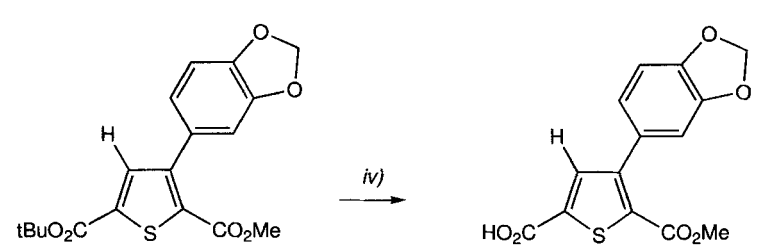
1e **9**

R^1= 2,3,4-$(MeO)_3C_6H_2$



1e **10**

R^1= 2,3,4-$(MeO)_3C_6H_2$



1g **11**

i) 95% aq. HCO_2H (*Method C*); *ii*) LiOH (3 equiv.), THF/MeOH/H_2O (3:1:1) (*Method D*); *iii*) PPTS, EtOH, 50° [13]; *iv*) CF_3CO_2H, CH_2Cl_2, H_2O (cat.).

Method C. To 3.0 mmol of the corresponding acetal **1a–c** in dioxane (5 ml) was added 95% aq. formic acid (10 ml) at 0°, and the mixture was stirred for 30 min at 0° and for 1–2 h at r.t. The solvents were removed under reduced pressure and the residue chromatographed or crystallized as indicated.

Method D. To a stirred soln. of the corresponding thiophenes **1b** and **1e** (3.0 mmol) in THF/MeOH/H_2O (3:1:1, 10 ml) was added at 0° LiOH · $1H_2O$ (378 mg, 9.0 mmol) in small portions. The mixture was stirred for 30 min at 0° and for 2–6 h at r.t., poured onto ice, 0.5M aq. HCl soln. (20 ml), and AcOEt (100 ml). The aq. layer was extracted with AcOEt (2 × 50 ml), the comb. org. fractions were washed with sat. brine (80 ml), dried ($MgSO_4$), the solvents removed, and the residue was crystallized from Et_2O/hexane.

Methyl 5-(Diethoxymethyl)-3-phenylthiophene-2-carboxylate (**1a**). From **4a** (2.5 g, 10.8 mmol) according to *Method B*: 2.87 g (83%) of **1a**. Colorless oil. IR (film): 3040*w*, 2976*m*, 2885*w*, 1725*s*, 1701*s*, 1549*w*, 1459*m*, 1374*w*, 1255*s*, 1214*m*, 1086*s*, 1055*s*, 756*m*, 697*m*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.5–7.35 (*m*, 5 arom. H); 7.07 (*d*, J = 0.8, 1 arom. H); 5.74 (*d*, J = 0.8, C*H*(OEt)$_2$); 3.76 (*s*, COOMe); 3.75–3.55 (*m*, MeC*H*$_2$); 1.26 (*t*, J = 7.1, *Me*CH$_2$). MS: 320 (22, M^+), 275(100), 247(40), 215(50), 115(20).

Methyl 5-(Diethoxymethyl)-3-(trifluoromethyl)thiophene-2-carboxylate (**1b**). From **4b** (2.0 g, 8.92 mmol) according to *Method B*, after chromatography on SiO_2 with hexane/AcOEt (1:6) and drying under reduced pressure: 2.2 g (79%) of **1b**. Solid. M.p. 52–53°. IR (KBr): 2975*w*, 1737*m*, 1655*w*, 1292*m*, 1260*s*, 1145*s*, 1087*s*, 1053*s*, 885*w*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.30 (*s*, 1 arom. H); 5.71 (*s*, C*H*(OEt)$_2$); 3.91 (*s*, COOMe); 3.75–3.5 (*m*, MeC*H*$_2$); 1.26 (*t*, J = 7.04, *Me*CH$_2$). MS: 267 (100, M^+), 239(60).

Methyl 5-(Diethoxymethyl)-3-[4-(methoxycarbonyl)phenyl]thiophene-2-carboxylate (**1c**). From **4c** (1.3 g, 4.48 mmol) according to *Method B*, after chromatography on SiO_2 with AcOEt/hexane (1:12 to 1:6): 1.39 g (82%) of **1c**. Colorless oil. IR (film): 2977*m*, 2952*w*, 2885*w*, 1723*s*, 1611*w*, 1457*m*, 1436*m*, 1278*s*, 1254*s*, 1172*m*, 1101*m*, 1055*m*, 1020*w*, 762*w*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 8.06, 7.51 (*2d*, *AA'BB'*, J_{AB} = 8.4, 4 arom. H); 7.07 (*s*, 1 arom. H); 5.74 (*s*, C*H*(OEt)$_2$); 3.94 (*s*, COOMe); 3.76 (*s*, COOMe); 3.75–3.55 (*m*, MeC*H*$_2$); 1.27 (*t*, J = 7.1, *Me*CH$_2$). MS: 378 (10, M^+), 333(100), 305(26), 273(10).

Methyl 5-(Diethoxymethyl)-3-pentylthiophene-2-carboxylate (**1d**). From **4d** (1.95 g, 8.62 mmol) according to *Method B*, after chromatography on SiO_2 (120 g) with AcOEt/hexane (1:10–1:5): 2.25 g (84%) of **1d**. Colorless oil. IR (film): 2978*w*, 2845*w*, 1713*s*, 1562*w*, 1273*m*, 1250*s*, 1099*s*, 1051*s*, 875*w*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 6.93 (*s*, 1 arom. H); 5.68 (*s*, C*H*(OEt)$_2$); 3.83 (*s*, COOMe); 3.75–3.5 (*m*, MeC*H*$_2$); 3.0–2.9 (*m*, 2 aliph. H); 1.7–1.55 (*m*, 2 aliph. H); 1.4–1.25 (*m*, 4 aliph. H); 1.25 (*t*, J = 7.1, *Me*CH$_2$); 0.95–0.85 (*m*, 3 aliph. H). MS: 314 (4, M^+), 269(100), 241(40).

Methyl 5-[(Tetrahydropyran-2-yloxy)methyl]-3-(3,4,5-trimethoxyphenyl)thiophene-2-carboxylate (**1e**). From **4e** (2.0 g, 5.38 mmol) according to *Method B*, after chromatography on SiO_2 (200 g) with AcOEt/hexane (1:4): 1.92 g (85%) of **1e**. Pale-yellow solid. M.p. 96–97°. IR (KBr): 3080*w*, 2916*m*, 2844*w*, 1721*s*, 1629*w*, 1584*s*, 1506*m*, 1463*m*, 1369*m*, 1243*s*, 1180*m*, 1125*s*, 1077*s*, 1031*s*, 843*w*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 6.99 (*s*, 1 arom. H); 6.69 (*s*, 2 arom. H); 4.90, 4.70 (*2d*, *AB*, J_{AB} = 13.1, 2H); 4.85–4.75 (*m*, CHO); 3.89 (*s*, 2 MeO); 4.0–3.85, 3.65–3.5 (*2m*, CH_2O); 1.95–1.5 (*m*, 6 aliph. H). MS: 422 (100, M^+), 321(35), 85(10). Anal. calc. for $C_{21}H_{26}O_7S$ (422.49): C 59.70, H 6.20, S 7.59; found: C 59.65, H 6.04, S 7.53.

Dimethyl 3-(3,4,5-Trimethoxyphenyl)thiophene-2,5-dicarboxylate (**1f**). From **4f** (820 mg, 2.95 mmol) according to *Method B*, after crystallization from Et_2O/hexane (1:2): 910 mg (84.2%) of **1f**. Pale-yellow solid. M.p. 146–147°. IR (KBr): 3010*w*, 2975*w*, 1727*s*, 1695*m*, 1582*m*, 1438*m*, 1414*m*, 1289*s*, 1241*m*, 1130*s*, 1088*m*, 1008*w*, 928*w*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.74 (*s*, 1 arom. H); 6.70 (*s*, 2 arom. H); 3.94, 3.90 (*2s*, 2 COOMe); 3.88 (*s*, 2 MeO); 3.83 (*s*, MeO). MS: 366 (100, M^+), 351(40). Anal. calc. for $C_{17}H_{18}O_7S$ (366.38): C 55.73, H 4.95, S 8.75; found: C 55.73, H 4.94, S 8.70.

*5-(*tert*-Butyl) 2-Methyl-3-(Benzo[1,3]dioxol-5-yl)thiophene-2,5-dicarboxylate* (**1g**). From **4g** (2.0 g, 7.79 mmol) according to *Method B*, after chromatography on SiO_2 (100 g) with AcOEt/hexane (1:10) and crystallization from Et_2O: 2.16 g (81.4%) of **1g**. Solid. M.p. 128–129°. IR (KBr): 3000*w*, 1728*s*, 1712*s*, 1629*w*, 1558*w*, 1503*w*, 1454*m*, 1281*m*, 1238*s*, 1209*m*, 1152*m*, 1093*w*, 770*w*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.59 (*s*, 1 arom. H); 6.95–6.8 (*m*, 3 arom. H); 6.00 (*s*, 2H); 3.81 (*s*, COOMe); 1.59 (*s*, COO(*t*-Bu)). MS: 362 (22, M^+), 306(100); 245(10). Anal. calc. for $C_{18}H_{18}O_6S$ (362.40): C 59.66, H 5.01; found: C 59.49, H 5.10.

*Methyl 5-{[(*tert*-Butoxycarbonyl)amino]methyl}-3-phenylthiophene-2-carboxylate* (**1h**). From **4h** (1.0 g, 3.86 mmol) according to *Method B*, after chromatography on SiO_2 (70 g) with AcOEt/hexane (1:4): 1.20 g (89.5%) of **1h**. Oil. IR (film): 3358*w* (br.), 2977*w*, 2951*w*, 1722*s*, 1698*s*, 1511*m*, 1456*m*, 1367*m*, 1251*s*, 1167*s*, 1077*m*, 756*w*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.45–7.3 (*m*, 5 arom. H); 6.94 (*s*, 1 arom. H); 5,00 (br. *s*, NH); 4.50 (br. *d*, J = 6.1, 2H); 3.75 (*s*, COOMe); 1.47 (*s*, *t*-Bu). MS: 347 (5, M^+), 316(5), 291(100), 276(38), 259(36), 246(30), 232(35).

Methyl 3-Phenyl-5-{[(triphenylmethyl)sulfonyl]methyl}thiophene-2-carboxylate (**1i**). From **4i** (2.06 g, 4.92 mmol) according to *Method B*, after chromatography on SiO_2 (100 g) with AcOEt/hexane (1:7 to 1:4) and

crystallization from Et_2O/hexane: 1.45 g (58%) of **1i**. Solid. M.p. 118–120°. IR (KBr): 3439*m* (br.), 3065*w*, 3040*w*, 2960*w*, 1720*s*, 1698*m*, 1492*m*, 1444*s*, 1369*w*, 1268*m*, 1232*m*, 1076*m*, 699*s*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.5–7.2 (*m*, 20 arom. H); 6.73 (*s*, 1 arom. H); 3.73 (*s*, COOMe); 3.51 (*s*, 2H). MS: 506 (< 1, $M^{+\cdot}$), 243(100), 165(10).

5,5-Diethoxy-1,1,1-trifluoropent-3-yn-1-one (**4b**). From **3a** (29.64 g, 0.231 mol) and freshly prepared CF_3CHO (**2b**) [13] according to *Method A*, after chromatography on SiO_2 with hexane/AcOEt (3:1 to 1:1): 34.7 g (67.0%) of **4b**. Colorless oil. IR (film): 2984*m*, 2937*m*, 2895*w*, 2265*w*, 2210*w*, 1720*s*, 1352*m*, 1222*s*, 1167*s*, 1127*s*, 1060*s*, 646*w*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 5.47 (*s*, C*H*(OEt)$_2$); 3.8–3.6 (*m*, MeCH_2); 1.27 (*t*, *J* = 7.1, *Me*CH$_2$). MS: 224 (< 1, $M^{+\cdot}$), 223(5), 179(90), 151(100), 103(30).

4,4-Diethoxy-1-[4-(methoxycarbonyl)phenyl]-but-2-yn-1-one (**4c**). From **3a** (5.0 ml) and *methyl 4-formylbenzoate* (**2c**; 7.44 g, 45.4 mmol) according to *Method A*, after chromatography on SiO_2 (700 g) with hexane/CH_2Cl_2: 6.54 g (64.4%) of **4c**. Colorless oil. IR (film): 2979*w*, 2889*w*, 2242*w*, 1728*s*, 1655*s*, 1437*w*, 1408*w*, 1283*s*, 1117*s*, 1054*s*, 720*m*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 8.25–8.1 (*m*, 4 arom. H); 5.53 (*s*, C*H*(OEt)$_2$); 3.96 (*s*, COOMe); 3.95–3.65 (*m*, 4H); 1.29 (*t*, *J* = 7.3, *Me*CH$_2$). MS: 290 (< 1, $M^{+\cdot}$), 259(10), 245(95), 217(100), 185(30), 163(30). Anal. calc. for $C_{16}H_{18}O_5$: C 66.20, H 6.25; found: C 66.10, H 6.27.

tert-*Butyl 4-(Benzo[1,3]dioxol-5-yl)-4-oxobut-2-ynoate* (**4g**). From **3d** (5.0 ml, 34.9 mmol) and piperonal (6.28 g, 41.9 mmol) according to *Method A*, after chromatography and crystallization from Et_2O/hexane: 7.85 g (82%) of **4g**. Solid. M.p. 74–75°. IR (KBr): 2950*w*, 2920*w*, 1708*s*, 1642*s*, 1601*s*, 1562*m*, 1527*m*, 1446*s*, 1371*m*, 1264*s*, 1153*s*, 1114*m*, 1036*m*, 745*m*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.85–7.75 (*m*, 1 arom. H); 7.55–7.5 (*m*, 1 arom. H); 6.90 (*d*, *J* = 8.2, 1 arom. H); 6.10 (*s*, 2H); 1.55 (*s*, *t*-Bu). MS: 274 (27, $M^{+\cdot}$), 218(100), 149(40). Anal. calc. for $C_{15}H_{14}O_5$ (274.27): C 65.69, H 5.15; found: C 65.78, H 5.30.

Methyl 5-Formyl-3-phenylthiophene-2-carboxylate (**7a**). From **1a** (910 mg, 2.84 mmol) according to *Method C*, after crystallization from Et_2O: 688 mg (98.4%) of **7a**. Solid. M.p. 115–116°. IR (KBr): 3070*w*, 3015*w*, 2970*w*, 2860*w*, 1725*s*, 1671*s*, 1555*w*, 1255*m*, 1235*s*, 1180*m*, 1077*w*, 759*w*, 698*w*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 9.98 (*s*, CHO); 7.71 (*s*, 1 arom. H); 7.44 (br. *s*, 5 arom. H); 3.82 (*s*, MeO). MS: 246 (100, $M^{+\cdot}$), 215(65), 115(30). Anal. calc. for $C_{13}H_{10}O_3S$ (246.28): C 63.40, H 4.09, S 13.02; found: C 63.40, H 4.07, S 12.99.

Methyl 5-Formyl-3-(trifluoromethyl)thiophene-2-carboxylate (**7b**). From **1b** (600 mg, 1.92 mmol) according to *Method C*, after chromatography on SiO_2 (50 g) with AcOEt/hexane (1:8) and crystallization from Et_2O/hexane: 430 mg (94%) of **7b**. Solid. M.p. 51.0–51.5°. IR (KBr): 3021*w*, 2962*w*, 1742*s*, 1685*s*, 1548*w*, 1459*w*, 1366*w*, 1268*s*, 1191*s*, 1167*s*, 1088*w*, 964*w*, 888*w*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 10.00 (*s*, CHO); 7.94 (*s*, 1 arom. H); 3.98 (*s*, COOMe). MS: 238 (65, $M^{+\cdot}$), 207(100), 179(10), 151(10). Anal. calc. for $C_8H_5F_3O_3S$ (238.18): C 40.34, H 2.12, S 13.46; found: C 40.24, H 2.16, S 13.45.

Methyl 5-Formyl-3-[4-(methoxycarbonyl)phenyl]thiophene-2-carboxylate (**7c**). From **1c** (800 mg, 2.11 mmol) according to *Method C*, after crystallization from Et_2O/hexane: 620 mg (96.5%) of **7c**. Solid. M.p. 179.5–181.0°. IR (KBr): 2970*w*, 1725*s*, 1703*s*, 1675*s*, 1612*w*, 1286*s*, 1255*m*, 1177*w*, 1120*w*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 9.99 (*s*, CHO); 8.11, 7.51 (2*d*, *AA'BB'*, J_{AB} = 8.5, 4 arom. H); 7.72 (*s*, 1 arom. H); 3.95 (*s*, COOMe); 3.82 (*s*, COOMe). MS: 304 (100, $M^{+\cdot}$), 273(98), 229(10). Anal. calc. for $C_{15}H_{12}O_5S$ (304.22): C 59.20, H 3.97, S 10.54; found: C 59.13, H 3.97, S 10.51.

5-(Diethoxymethyl)-3-(trifluoromethyl)thiophene-2-carboxylic Acid (**8**). From **1a** (2.11 g, 6.47 mmol) according to *Method D*, after crystallization from Et_2O: 1.85 g (95.9%) of **8**. Solid. M.p. 90–92°. IR (KBr): 3435*w* (br.), 2979*m*, 2901*w*, 1713*s*, 1679*m*, 1557*w*, 1489*m*, 1469*m*, 1320*s*, 1283*s*, 1163*s*, 1062*s*, 873*m*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 10.00 (br. *s*, COOH); 7.33 (*s*, 1 arom. H); 5.73 (*s*, C*H*(OEt)$_2$); 3.8–3.55 (*m*, MeCH_2); 1.27 (*t*, *J* = 7.1, *Me*CH$_2$). MS: 298 (2, M^+), 253(100), 225(84), 185(20). Anal. calc. for $C_{11}H_{13}F_3O_4S$ (298.28): C 44.30, H 4.39, S 10.75; found: C 44.05, H 4.28, S 10.70.

5-[(Tetrahydropyran-2-yloxy)methyl]-3-(3,4,5-trimethoxyphenyl)thiophene-2-carboxylic Acid (**9**). From **1e** (620 mg, 1.48 mmol) according to *Method D*, after crystallization from Et_2O/hexane: 560 mg (93.1%) of **9**. Solid. M.p. 145–146°. IR (KBr): 3446*w* (br.), 3080*w*, 2948*m*, 2640*w*, 1673*s*, 1585*s*, 1508*m*, 1471*s*, 1287*m*, 1129*s*, 1025*m*, 834*w*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.01 (*s*, 1 arom. H); 6.69 (*s*, 2 arom. H); 4.92, 4.70 (2*d*, *AB*, J_{AB} = 13.2, 2H); 4.85–4.75 (*m*, CHO); 3.90 (*s*, MeO); 3.86 (*s*, 2 MeO); 4.0–3.85, 3.65–3.55 (2*m*, 2H); 1.95–1.5 (*m*, 6 aliph. H). MS (ISN): 407.1 (100, [*M* – H]), 362.2 (45). Anal. calc. for $C_{20}H_{24}O_7S$ (408.47): C 58.81, H 5.92, S 7.85; found: C 58.71, H 5.91, S 7.64.

Methyl 5-(Hydroxymethyl)-3-(3,4,5-trimethoxyphenyl)thiophene-2-carboxylate (**10**). A mixture of **1e** (1.0 g, 2.38 mmol) and 120 mg (0.48 mmol) pyridinium *p*-toluenesulfonate (PPTS) in dioxane/EtOH (2:3, 5 ml) was stirred for 4 h at 50°, cooled to r.t., and extracted with H_2O and AcOEt. The org. layer was washed with sat. brine (15 ml), dried ($MgSO_4$), and the solvents were removed. The residue was precipitated from Et_2O/hexane: 765 mg (95%) of **10**. Solid. M.p. 139–140°. IR (KBr): 3502*s*, 3025*w*, 2970*w*, 1718*m*, 1685*s*, 1589*m*, 1507*m*, 1460*m*, 1243*s*,

1134*s*, 1014*w*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.01 (*s*, 1 arom. H); 6.69 (*s*, 2 arom. H); 4.86 (*d*, $J = 6.1$, CH_2OH); 3.90 (*s*, COOMe); 3.87 (*s*, 2 MeO); 3.79 (*s*, MeO); 2.00 (*t*, $J = 6.1$, OH). MS: 338 (100, $M^{+\cdot}$), 323(39).

5-(Methoxycarbonyl)-4-(Benzo[1,3]dioxol-5-yl)thiophene-2-carboxylic Acid (**11**). To a stirred soln. of **1g** (1.50 g, 4.14 mmol) in CH_2Cl_2 (10 ml) was added at 0° CF_3COOH acid (10 ml) and a few drops of H_2O. The mixture was stirred for 30 min at 0° and for 3 h at r.t., the solvents were removed, and the residue was precipitated from Et_2O/hexane: 1.25 g (98.6%) of **11**. Solid. M.p. < 245° (dec.). IR (KBr): 2970*w*, 2960*w*, 1731*s*, 1691*s*, 1555*w*, 1464*s*, 1451*m*, 1299*w*, 1255*m*, 1238*s*, 1210*m*, 1044*w*, 769*w*. ^{1}H-NMR ((D_6)DMSO, 250 MHz): 13.75 (br. *s*, COOH); 7.67 (*s*, 1 arom. H); 7.05–6.9 (*m*, 2 arom. H); 6.07 (*s*, 2H); 3.75 (*s*, COOMe). MS: 306 (< 100, $M^{+\cdot}$), 245(15), 217(15). Anal. calc. for $C_{14}H_{10}O_6S$ (306.29): C 54.90, H 3.29, S 10.47; found: C 54.67, H 3.30, S 10.36.

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